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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/800,361	03/11/2004	Peter William Gage	17136-002RE1	7939
26181	7590	01/05/2006	EXAMINER	
FISH & RICHARDSON P.C. PO BOX 1022 MINNEAPOLIS, MN 55440-1022			HUMPHREY, LOUISE WANG ZHIYING	
			ART UNIT	PAPER NUMBER
			1648	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/800,361

Applicant(s)

GAGE ET AL.

Examiner

Louise Humphrey, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 November 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1-8, 10, 15 and 20 is/are allowed.
- 6) ☒ Claim(s) 9, 11-14, 16-19, 21 and 22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03/11/2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>14 November 2005</u> . | 6) <input type="checkbox"/> Other: _____ |

Reissue Applications

The examiner of your application in the Patent and Trademark Office has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Louise Humphrey, Art Unit 1648.

This Office Action is in response to the amendment filed on 14 November 2005. Claims 1-23 are pending. Claims 9, 11-14, 16-19, 21 and 22 are under final rejection. Claims 1-8, 10, 15, and 20 are allowable.

Information Disclosure Statement

The information disclosure statement (IDS) filed on 14 November 2005. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

The objection to the Oath and Declaration is **withdrawn** in view of the Applicants' newly filed Oath and Declaration on 14 November 2005.

The rejection of claims 1-23 under 35 U.S.C. §251, as being improperly broadened in a reissue application made and sworn to by the assignee and not the patentee is **withdrawn** in view of the Supplemental Reissue Declaration.

Applicants' arguments filed on 14 November 2005 have been fully considered but they are not persuasive for the following reasons:

The rejection of claims 9, 11, 12, 14, 16, 17, 19, 21, and 22 under 35 U.S.C. §103(a) as being unpatentable over Harpold *et al.* (US 5,846,757), later referred to as the '757 patent, and Schubert *et al.* (American Society for Microbiology. 1995, page 63) **is maintained.**

Applicants argue that the '757 patent (1) does not teach or suggest screening a test substance having potential for modulating the activity of any viral protein, let alone the ion channel activity of HIV-1 Vpu; (2) is directed to Ca^{2+} channel proteins, which are native to the plasma membrane in some bacterial, fungal, and plant cells; (3) typically employs complex, delicate analytical apparatus and can be too tedious and time-consuming for routine screening of ion channel activity; and (4) teaches measurement of ion channel activity via intracellular detection of a large indicator protein...the claimed method measures ion channel activity indirectly through changes in permeability of the plasma membrane of the host cell to small cellular metabolite molecule...and does not require the complex electrophysiological or intracellular methods taught by the '757 patent and eliminates the depolarization step of the patent... Applicants subsequently argue that (5) Schubert *et al.* refer to electrophysiology and provide no additional teaching regarding ion channel activity measurement beyond that of the '757 patent. Applicants further argue that (6) "Schubert *et al.* and the '757 patent do not teach or suggest heterologous expression of HIV-1 Vpu integral membrane protein in the plasma

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membrane...there is no teaching that HIV-1 Vpu expressed outside its native membrane would fold correctly or retain its native ion channel activity. Thus, there is no reasonable expectation of success.” Applicants argue that (7) “the Schubert *et al.* reference does not teach or suggest a test substance having potential for ion channel modulating activity, let alone a screening method for determining the modulating ability of such a substance on HIV-1 Vpu.” Applicants finally argue that (8) both the ‘757 patent and Schubert *et al.* reference are silent regarding “small cellular metabolite molecules” and that the term “small cellular metabolite molecules” is distinct from the Ca^{2+} or Ba^{2+} ions employed in the ‘757 patent.

In response to Applicants’ arguments (1) and (2) against the ‘757 patent reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The prior Office Action clearly pointed out on page 3, in the third paragraph, that the ‘757 patent teaches a method determining whether a test substance modulates the activity of the heterologous calcium channel and the permeability of the cell plasma membrane. The prior Office Action specifically noted that the ‘757 patent does not teach HIV Vpu. However, Schubert *et al.* teach heterologous HIV-1 Vpu ion channel activity in artificial lipid bilayers, see the meeting abstract provided.

In response to Applicants’ arguments (3) and (4) against the ‘757 patent, it is noted that the features upon which applicants rely (i.e., the employed apparatus and the

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methods of ion channel activity measurement) are not recited in the rejected claims.

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Besides the irrelevance of these features to the limitations of the rejected claims, it is obvious to one skilled in the art to modify the methods of measurement, as disclosed in the '757 patent, to the simple biochemical method steps in the instant invention with reasonable expectation of success. The reason is set forth below.

In response to Applicants' argument (5) about teachings regarding ion channel activity measurement, the Applicants selectively cite that Schubert *et al.* refer to electrophysiology but apparently disregard the fact that Schubert *et al.* also refer to biochemistry, which is the method disclosed in the current specification and, as admitted by the Applicants themselves, is well-established in the prior art. See column 8, line 30.

In response to Applicants' argument (6) that there is no suggestion or reasonable expectation to success to combine the references, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Schubert *et al.* teaches that HIV-1 Vpu is an integral membrane

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phosphoprotein and transmembrane (TM)-domain, which is in the plasma membrane of a cell, by definition in any cell biology textbook. Further, presence in the plasma membrane is a pre-requisite for ion channel activity. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). According to M.P.E.P. § 2143.02, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)." Applicant has not presented any evidence showing that there was no reasonable expectation of success.

In response to Applicants' argument (7) against the Schubert *et al.* reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As indicated in the prior Office Action, the Examiner cited Schubert *et al.* to meet the limitation of "HIV-1 Vpu protein" in the rejected claims, not to meet the limitations of "a screening method for determining the modulating ability of a test substance having potential for ion channel modulating activity", which are already addressed by the '757 patent.

In response to Applicants' argument (8) that both the '757 patent and Schubert *et al.* reference are silent regarding "small cellular metabolite molecules," Applicants' assertion that the "small cellular metabolite molecules" are distinct from the Ca^{2+} ions taught in the '757 patent is unsubstantiated and contradicted by their later argument, when differentiating between the ion channel proteins and aromatic transport proteins of the '852 patent, listing Ca^{2+} and Ba^{2+} in the '757 patent as examples of the atomic ions selected for by ion channel proteins. The instant invention is a screening method for a modulator of an ion channel, which functions by regulating the permeability of the plasma membrane of the host cell to small cellular metabolite molecules. By the definition in a cell biology textbook, Ca^{2+} channels are ion channels, the same as are Na^+/K^+ channels, as exemplified by the current specification. See column 4, line 30. Therefore, "small cellular metabolite molecules" is an inherent feature of ion channel activity. The recited limitation is "detecting the effect of the test substance on changes in net movement across the plasma membrane of the host cell of small cellular metabolite molecules," which is met by the assays taught in the art, as indicated in the prior Office Action. Therefore, this argument is out of context and contradicted by the Applicants themselves.

Therefore, the Applicant has not provided any compelling reason or evidence to overcome the obviousness rejection under 35 U.S.C. §103 over Harpold *et al.* (the '757 patent) and Schubert *et al.*

The rejection of claims 13, 18, and 23 under 35 U.S.C. §103, as being obvious over Harpold *et al.* (the '757 patent) and Schubert *et al.*, further in view of Tribe, US 4,681,852 **is maintained**.

In response to Applicants' argument that "the '852 patent's teaching of aromatic transport proteins is not relevant to ion channel proteins... there is substantial differences in sequence, structure and function between ion channel proteins and aromatic transport proteins... the '757 patent does not teach transport (leakage) of small metabolite molecules... the '852 patent does not teach that cross-feeding can determine changes to the ion channel activity of a heterologous protein induced by a test substance" to reach the conclusion that "there is no motivation to combine the '757 patent and the '852 patent," the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicants' interpretation that "the '852 patent specifically teaches away from a functional relationship between the common aromatic transport system and atomic ions... the '852 patent teaches that there is no functional relationship between the common aromatic transport system and atomic ions similar to those selected for by the ion channel proteins in the '757 patent" is spurious. Applicants seem to have misconstrued the meaning of the two pieces of evidence presented in the '852 patent –

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there is “no apparent iron effect on either cell growth or phenylalanine output over the range of ferric chloride concentrations tested” and “the effect of adding a range of cobaltous chloride concentrations to culture medium was examined but no clear evidence was obtained that this parameter has any effect on phenylalanine yield” – in order to detect the absence of ion channels, which meets the limitation “failure of cell expressing the ion channel to grow in the absence of the leaking metabolite being supplied in the external medium” in the rejected claims. As indicated in the prior Office Action, at the bottom of page 4, the ‘852 patents motivates by teaching that cross-feeding autotrophic cells is useful for identifying mutant cells with a particular loss of a relevant transport system, which is the ion channel in this case.

Applicants’ argument that there would not have been a reasonable expectation of success is moot because Applicants have not presented any evidence showing that there was no reasonable expectation of success. According to M.P.E.P. §2143.02, “Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976).

The suggestion to combine or modify the teaching of the prior art can be established either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). To establish a *prima facie* case of obviousness, the Board must, *inter alia*, show “some

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objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.” *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). “The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved.” *In re Kotzab*, 217 F.3d at 1370, 55 USPQ2d at 1317.

The last paragraph of Applicants’ traversal is a mere assertion that “even in combination, the ‘757 patent, the Schubert *et al.* reference and the ‘852 patent still do not teach or suggest the claimed step of determining the changes to the ion channel activity...” and is not supported by any evidence or objective reasoning.

Therefore, the Applicant has not provided any compelling reason or evidence to overcome the obviousness rejection under 35 U.S.C. §103, over Harpold *et al.* (the ‘757 patent) and Schubert *et al.*, further in view of Tribe (the ‘852 patent).

Allowable Subject Matter

Claims 1-8 are drawn to allowable subject matter. The prior art does not teach or suggest monitoring metabolites that do not directly permeate the ion channel formed by a heterologous protein in the plasma membrane of the cell.

In addition, claims 10, 15 and 20 are also drawn to allowable subject matter. The claims are drawn to determining the effect of permeability of proline or adenine across the plasma membrane. One of ordinary skill in the art at the time the invention was

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made would not have had a reasonable expectation of detecting the influx of proline or adenine into and out of a cell through the heterologous HIV-1 Vpu of Schubert *et al.* because it was unknown that proline or adenine passed through the HIV-1 Vpu channel at the time the invention was made. Schubert *et al.* only teach that HIV-1 Vpu has ion channel activity. The reference does not teach which ions pass through the channel and since neither proline nor adenine is an ion, it would not be expected that these molecules would be conveyed through the Vpu ion channel.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Contact Information

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Louise Humphrey, Ph.D.
29 December 2005


JEFFREY STUCKER
PRIMARY EXAMINER